

physiological methods and validated questionnaires. Ten single nucleotide polymorphisms (SNPs) have previously been suggested to be predictive of late radiation induced toxicity by GWAS studies or candidate gene studies. The objective of this study was to test the ten SNPs in this unique cohort. The strength of the reportings as well as the clinical data available served as the rationale for using our rather small cohort as a validation cohort.

Materials and Methods: The patients in this cohort have received EBRT 70-78 Gy for prostate cancer with curative intent. Functional toxicity endpoints have been examined by sigmoidoscopy, manometry, endoanal ultrasonography and impedance planimetry in an earlier study. Objective endpoints include the Vienna Rectoscopy Score (VRS), cross sectional area (CSA) of rectum at distension, maximum resting pressure (MRP) and maximum squeezing pressure (MSP) of anal sphincters. The subjective measure RT-Anorectal dysfunction score (RT-ARD) was obtained from the questionnaires. Biological material from the patients in this cohort is available from an established research biobank. The SNPs were investigated in DNA from fibroblasts with TaqMan SNP assays. Statistical analyses was carried out with Stata13. For each SNP (table I) the reported risk allele was identified and due to the small sample size a risk-allele average was created for each patient. This risk-allele average was correlated to RT-ARD, VRS, MRP, MSP and CSA by Spearman's rank correlation.

Table I. Tested SNPs and gene relation.

SNP	Gene
rs264663	TANC1
rs17630638	Near SLC36A4
rs1800629	TNF
rs1800469	TGFB1
rs2268363	FSHR
rs3738000	NEK11
rs1801516	ATM
rs13035033	MYO3B
rs7120482	Near SLC36A4
rs17779457	IFNK / MOB3B

Results: All SNPs in the cohort were in Hardy-Weinberg equilibrium. Preliminary results showed no statistically significant correlations between the risk-allele average and toxicity end points tested. Spearman's rank correlations ρ (rho) were as follows: VRS $\rho = 0.17$ $p = 0.33$, MRP $\rho = -0.08$ $p = 0.64$, MSP $\rho = 0.02$ $p = 0.91$, CSA $\rho = 0.03$ $p = 0.88$, RT-ARD $\rho = -0.26$ $p = 0.13$.

Conclusions: Preliminary results indicate no correlation between risk-allele average and late radiation toxicity end points tested. The cohort will be expanded with 234 patients having received the same treatment and with the same questionnaire data on morbidity.

OC-0085

Mitochondrial DNA variation as a biomarker for the development of radiation-induced lung toxicity

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Purpose/Objective: Radiation-induced lung toxicity (RILT) varies significantly between patients at similar doses to the lung and can seriously affect the quality of life. The identification of prognostic biomarkers for radiation-induced toxicity is crucial for personalized RT: to select patients for proton therapy or dose escalation. We hypothesized variation in the mitochondrial genome (mtDNA) is a biomarker for RILT, since mitochondria and RT have several processes in common, among which reactive oxygen species (ROS) production.

Materials and Methods: Blood DNA was isolated from 372 (training set, Maastricht) and 68 (test set, Ghent) lung cancer patients. After exclusion of patients that had surgery, had other tumors within 5 years prior to lung cancer, received a palliative dose or for which baseline dyspnea score was unknown, 277 and 53 patients were remaining for the training and test set respectively. Baseline dyspnea (at the start of RT) and maximal dyspnea 3-6 months after RT were scored according to the CTCAE version 3.0 criteria. The endpoint of analysis was dyspnea grade ≥ 2 after RT. Additionally, DNA was obtained from fibroblasts of 21 breast cancer patients for which the toxicity grade after radiotherapy was known (LENT/SOMA criteria). mtDNA was resequenced using mitochips and homoplasmic deviations from the revised Cambridge reference sequence were recorded. Variants were classified into 7 functional categories based on their theoretical effect on OXPHOS function.

Results: Using the 7 functional categories as input features, logistic regression analysis corrected for baseline dyspnea score resulted in an AUC of 0.78 for the training set, which was significantly better than the current international gold standard Mean Lung Dose (AUC 0.57; $p < 0.001$). The AUC for the test set was 0.66 but the power of the validation was limited due to the small sample size. Validation in a second external test set is ongoing. Additionally, using mtDNA variation data we were able to classify breast cancer patients in the correct toxicity group with 80% accuracy.

Conclusions: Our data showed that mtDNA variation is a valuable biomarker for RILT. Furthermore, we have preliminary data in breast cancer patients that the predictive effect of mtDNA might be applicable to radiation toxicity in general.

Proffered Papers: Brachytherapy 2: Prostate HDR

OC-0086

Dosimetric inter- and intra-observer contouring and registration variability for prostate brachytherapy

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Purpose/Objective: (1) To quantify the geometric and dosimetric variability of prostate contouring on US for low-dose-rate brachytherapy. (2) To assess the dosimetric variability of registrations of T1-weighted MRI with C-arm cone beam CT (CBCT) and the currently performed US-CBCT registrations.

Materials and Methods: VariSeed studies of eleven patients previously treated with low-dose-rate brachytherapy at our institute were enrolled in a multi-observer study. Six observers performed three sessions of prostate contouring on US and registrations of US- and MRI-CBCT.

Prostate contours were sampled at 10 degree increments of the polar and azimuthal angles from the center of mass. The

radial distances were compared to those of the clinically used contours (inter-observer) and the average contours per patient and observer (intra-observer). The registration process was initiated with the localization of gold fiducial markers (FMs) and, if necessary, adjusted manually for rotation and/or translation. Prostate V100 and D90 were determined for each contour and registration. The two dosimetric parameters (DPs) were scaled with the patients clinical DPs (inter, see Figure 1) or the patients average per observer (intra) to remove the natural variation in DPs between patients.

Results: Prostate contours on US resulted in an inter-observer variability of 1.1 mm (1 SD with respect to the clinical contours) and an intra-observer variability of 0.6 mm (1 SD with respect to the average contour per patient and observer). US-contouring alone led to dosimetric differences of 1.6% of the clinical V100 and 9.3% of the clinical D90, and an intra-observer variability of 0.6% (V100) and 1.0% (D90). US-CBCT registrations varied within 2.0% of the clinical V100 and 3.1% of the clinical D90. For MRI-CBCT registration, this was 1.3% and 2.1% respectively. The intra-observer variabilities of US-CBCT (V100: 0.9% and D90: 1.5%) and MRI-CBCT (V100: 0.7% and D90: 1.0%) registration were smaller than the inter-observer variabilities. During registration, observers found 91% of the FMs on US, 100% on CBCT and 99% on MRI. 78% of the US-CBCT registrations were manually adjusted based on the urethra contours and iodine seeds. MRI-CBCT registrations were manually adjusted in 18% of the studies.

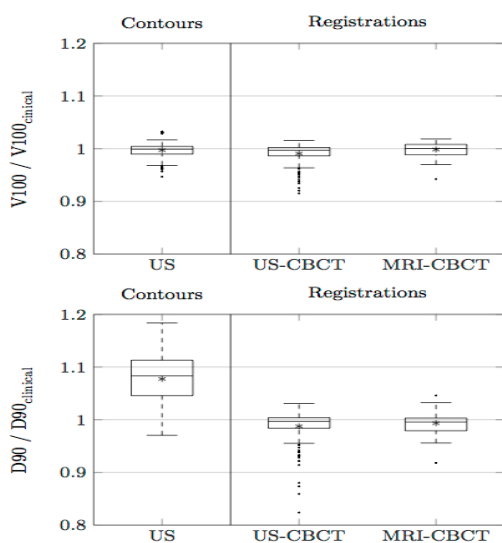


Figure 1: V100 (top) and D90 (bottom), scaled by the respective clinical parameters, originating from observer contours on US and US- and MRI-CBCT registrations. The symbol (*) is displayed at the observer mean.

Conclusions: US- and MRI-CBCT registrations showed little variability compared to the inter-observer variability in US-contouring. Inter-observer contouring caused D90 variations of 9.3% from the clinical value. The intra-observer contouring variability was comparable to the registration variability. Good FM visibility on MRI scans resulted in small registration variabilities. The inferior FM visibility on US was compensated by the manual adjustment based on seeds and urethra.

OC-0087

HDR brachytherapy combined with interstitial hyperthermia for prostate cancer - tolerance and toxicity
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Purpose/Objective: Evaluation of tolerance, early and late toxicity of HDR brachytherapy combined with interstitial hyperthermia (IHT) in patients treated for prostate cancer.

Materials and Methods: 105 patients were treated for prostate cancer using HDRBT combined with IHT. 79 patients were treated for primary prostate adenocarcinoma, and 26 patients for local recurrence after previous definitive EBRT. The treatment of 76 patients consisted of external beam radiotherapy (EBRT) to the total dose of 50 Gy and HDRBT boost (21Gy in 2 fractions), 3 patients received HDRBT as a monotherapy to the total dose of 45 Gy in 3 fractions. Salvage HDRBT for local cancer recurrence was performed to the total dose of 30 Gy in 3 fractions. IHT was planned before each HDRBT fraction to the temperature of 40-43°C for 60 minutes. Toxicity was assessed according to Common Toxicity Criteria for Adverse Events version 4.03.

Results: The median follow-up time was 26.4 months (range 7 - 61 months). We didn't observe any grade 3 or higher gastrointestinal (GI) or genitourinary (GU) early toxicities. Early GU grade 1 and 2 toxicities were common, but only two patients (1,9%) experienced acute urethral stenosis and required temporary catheterisation (grade 2). Only two patients (1,9%) developed late grade 3 urinary tract obstruction with urinary retention, which required transurethral resection of the prostate (TURP). The incidence of grade 2 toxicity in this group of patients did not exceed 30%. There were no late grade 2 or higher complications from the gastrointestinal tract. There were no statistically significant differences in early complications between the groups of patients treated with radical and salvage intent, except for haematuria ($p < 0.01$) and rectal bleeding ($p < 0.01$).

Conclusions: The combination of HDRBT with IHT is well tolerated. The profile of early and late complications is acceptable, while the incidence of grade 3 toxicity remained within a few percent only.

OC-0088

Evaluation of dose-predictors of urethral strictures for prostate patients treated with HDR brachytherapy

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Purpose/Objective: High Dose-Rate brachytherapy (HDRB) for the treatment of prostate cancer provides biochemical control comparable to other treatment modalities with the benefit of reducing dose to the OARs. Generally delivered in conjunction with external beam radiotherapy HDRB has the potential advantage of allowing dose escalation due to the high dose delivered during the treatment fraction. However, the wide ranges of fractionation regimes used in different centres make it difficult to establish clear guidelines for